

Increase the risk of intellectual disability in children with scabies

A nationwide population-based cohort study

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Abstract

Scabies is a common and distressing disease caused by the mite *Sarcoptes scabiei* var. *hominis*. Psychiatric disorder in childhood is an important disease and easily neglected. There are several similarities in scabies and psychiatric disorders in childhood (PDC). Both of them may present with pruritus. They are relatively common in patients with lower socioeconomic status and crowded environment. Furthermore, immune-mediated inflammatory processes play a role in the pathophysiology in both diseases. An association between scabies and psychiatric disorders may exist. This nationwide population-based cohort study utilized data from the National Health Insurance Research Database to investigate the relationship between scabies and PDC. A total of 2137 children with scabies were identified as the study group and 8548 age- and sex-matched children were selected as the control group. A total of 607 (5.68%) children developed PDC during the 7-year follow-up period. The overall incidences of PDC are similar but patients with scabies had a higher risk of developing intellectual disability (ID) (scabies group vs control group: 1.3% vs 0.6%, adjusted hazard ratio: 2.04 and 95% confidence interval: 1.25–3.32). The immune-mediated inflammatory processes of both diseases were reviewed and may contribute to the 104% increased risk of interleukin in patients with scabies. We suggest a more comprehensive management in treating patients with scabies or ID. Early and comprehensive treatment of scabies and other risk factors may decrease the risk of subsequent ID. When we approach patients with ID, concurrent evaluation of scabies and other risk factors may contribute to successful management.

Abbreviations: ADHD = attention deficit hyperactivity disorder, aHR = adjusted hazard ratio, CI = confidence interval, ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification, ID = intellectual disability, IL = interleukin,

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LHID2000 = Longitudinal Health Insurance Database 2000, NHIRD = National Health Insurance Research Database, OCD = obsessive-compulsive disorder, PDC = psychiatric disorders in childhood.

Keywords: childhood psychiatric disorder, children, intellectual disability, mental disorder, mental health, National Health Insurance Research Database, scabies

1. Introduction

Scabies is a common and distressing disease caused by the mite *Sarcoptes scabiei* var. *hominis*.^[1] The disease burden is substantial and affects between 0.2% and 71.4% of the general population depending on the region.^[1–3] Scabies is most prevalent during early childhood with a peak age between 5 and 9 years old.^[3] The skin lesions are intensely pruritic, and a scabies infection can profoundly impair the individual's quality of life. The pruritus is more severe at night, and thus, sleep disturbance and inattention are common in children with scabies. In addition, an infestation of *S. scabiei* var. *hominis* will induce immune-mediated inflammatory reactions, and some systemic diseases have been associated with scabies.^[4–6] However, the precise mechanism and long-term consequences of a scabies infection remain largely unclear.

At least 1 in 10 children have a psychiatric disorder.^[7,8] However, psychiatric disorders in childhood (PDC) are difficult to diagnose and are underestimated worldwide.^[8] Various diseases, including neurologic and developmental diseases, may present as psychiatry disorders, the manifestations of which may initially be occult.^[9] In addition, the environmental, family education status, and socioeconomic factors have a huge impact on the clinical manifestation of the affected individual. Moreover, inattention, sleep disturbance, and somatic complaints are common in children.^[10,11] Although advances in the understanding of psychiatric disorders (e.g., the roles of neurotransmitters and cytokines in the pathophysiology of psychiatric disorders) have been made, the diagnosis of PDC remains a challenge for both pediatricians and psychiatrists.^[12]

There are several similarities for both diseases and an association between these 2 diseases may exist. For example, both diseases may present as pruritus, inattention, and sleep disturbances.^[1,13] Pruritus is one of the most common somatic symptoms and can lead to the diagnosis of several psychiatric disorders. In addition, both scabies and PDC are prevalent in patients with a lower socioeconomic status.^[14–16] Third, immune-mediated inflammation plays a role in the underlying pathophysiology.^[5,12] The association between scabies and PDC has not been previously reported in the literature. Therefore, we hypothesized that there was an association between an infection with scabies and PDC. Specifically, an infection with scabies during childhood may increase the subsequent risk of psychiatric disorders in adolescents. We conducted the nationwide population-based cohort study to investigate the relationship between scabies and PDC.

2. Materials and methods

2.1. Database

This large-scale study utilized data from the National Health Insurance Research Database (NHIRD) of Taiwan, which was a unique public health and medical insurance system. The National Health Insurance program was launched in 1995 and covered 99.9% of the 23 million residents of Taiwan by the end of 2013.^[17] The NHIRD includes all data for persons seeking

medical aid, including demographic data, medical records, and medical procedures. We used the Longitudinal Health Insurance Database 2000 (LHID2000), which consists of a sub-dataset of the NHIRD-comprised data from 1 million people randomly selected from the larger NHIRD in 2000 and representative of the nationwide population.^[18]

2.2. Study subjects

The study subjects were chosen from LHID2000 and the study period was between January 2000 and December 2013. This study was divided into 2 stages: first, recruiting patients with newly diagnosed scabies and matched controls, and second, the follow-up of newly developed PDC. The diagnoses of the patients were sorted according to The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system.^[19] The patients newly diagnosed with scabies (ICD-9-CM: 133.0) by licensed doctors between 2001 and 2006 were enrolled in this study (Fig. 1). The exclusion criteria consisted of patients who were diagnosed with scabies before January 1, 2001 (n=1087); patients with missing medical records (n=125); patients older than 18 years (n=8478); and patients with history of scabies or any PDC (n=141). Finally, a total of 2137 patients with a scabies infection were enrolled as the scabies groups. Patients without scabies were enrolled by randomly matching patients by gender, age, insured region, and urbanization to the scabies group at a ratio of 1:4 as the control group. Specifically, the nonscabies control group patients were matched by age (0–2, 3–5, 6–12, and 13–18 years), gender, and index year of the scabies diagnoses of the patients in the scabies group. A total of 8548 subjects were enrolled in the nonscabies control group. Subjects who had a previous psychiatric history (ICD-9-CM: 290–319) were excluded from both the study and control groups.

A total of 10,685 subjects were enrolled in the study, including 2137 study subjects in the scabies group and 8548 study subjects in the nonscabies control group. We tracked each subject over a 7-year period starting with their index date to determine which subjects were diagnosed with PDC, based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,^[20] which included attention deficit hyperactivity disorder (ADHD) (ICD-9-CM:314), autism spectrum disorder (ICD-9-CM: 299), anxiety (ICD-9-CM: 300 except 300.3, 300.4), schizophrenia (ICD-9-CM: 295), intellectual disability (ID) (ICD-9-CM: 317–319), tic disorder (ICD-9-CM: 307.2), delayed development (ICD-9-CM: 315), obsessive-compulsive disorder (OCD) (ICD-9-CM: 300.3), conductive disorder (ICD-9-CM: 312), disturbance of emotions specific to childhood and adolescence (ICD-9-CM: 313), psychic factors associated with diseases (ICD-9-CM: 316), eating disorder (ICD-9-CM: 307.5), stuttering (ICD-9-CM: 307.0), communication disorder (ICD-9-CM: 307.9), enuresis (ICD-9-CM: 307.6), encopresis (ICD-9-CM: 307.7, 787.6), and separation anxiety disorder (ICD-9-CM: 309.21) during the follow-up period. Disturbance of emotions specific to childhood and adolescence (ICD-9-CM: 313) comprised the different types of emotional disturbances in childhood and adolescence:

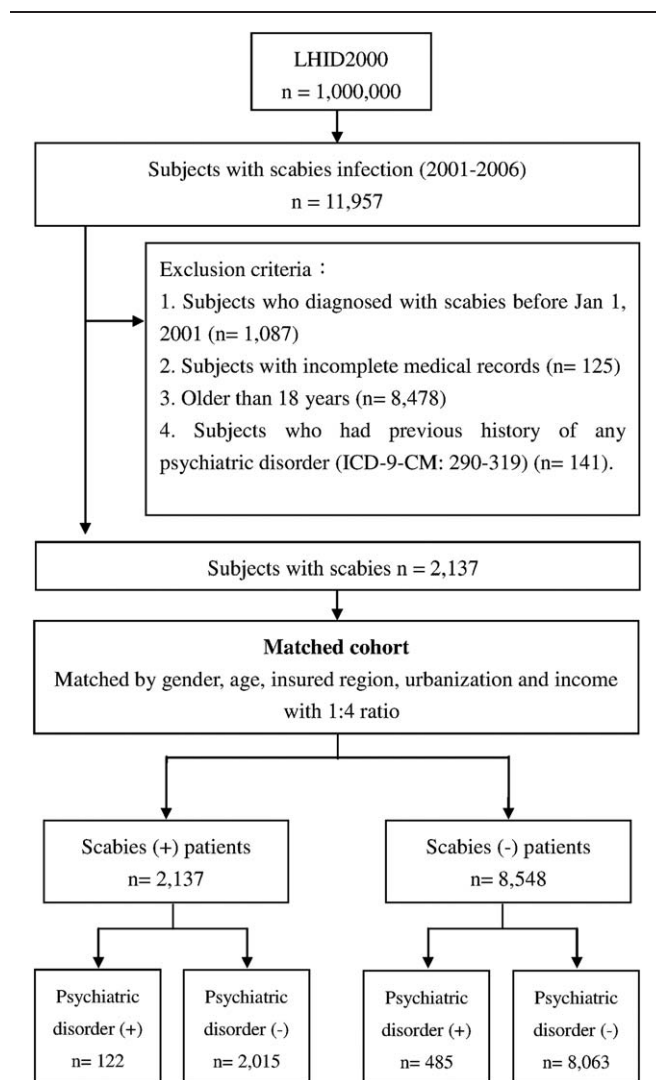


Figure 1. Flowchart of recruitment of subjects from the 1 million random sample of the National Health Insurance Research Database from 2000 to 2006 in Taiwan.

overanxious, misery and unhappiness, shyness, introverted disorders, and so on. Mental disturbances or psychic factors which were thought to have played a major part in the etiology of physical conditions were classified in psychic factors associated with diseases (ICD-9-CM: 316), such as psychogenic asthma, dermatitis, and gastric ulcer. Enuresis (ICD-9-CM: 307.6) was considered as physiological disorder before the age of 3 years and encopresis (ICD-9-CM: 307.7, 787.6) was regarded as physiological disorder before the age of 4 years.^[20]

The outcomes of this study included the number of patients newly diagnosed with any PDC in each group. We also identified and analyzed all the other medical diagnoses and procedures of the patients during the follow-up period. The diagnoses of PDC were made by psychiatrists on the basis of at least 1 admission or at least 2 consistent diagnoses in outpatient departments due to the diseases mentioned above. In addition, PDC was diagnosed by the psychiatrists according to a detailed clinical interviews and based on their experimental judgment with the aim of achieving diagnostic validity.

This study was approved by the Institutional Review Board of the Tri-Service General Hospital (approval number: TSGHIRB

NO. B-105-06.). As this was a retrospective study and all data was anonymous, the Institutional Review Board committee agreed with the authors that it was not necessary to obtain patient consent.

2.3. Adjustment of covariates

The covariates of the comorbidities selected in this study consisted of asthma (ICD-9-CM: 493), atopic dermatitis (ICD-9-CM: 691), allergic rhinitis (ICD-9-CM: 477), and preterm labor (ICD-9-CM: 765.0, 765.1). Age was categorized into 4 age groups: 0 to 2, 3 to 5, 6 to 12, and 13 to 18 years. Urbanization was classified into 4 groups. The geographic areas of residency in Taiwan were divided into 4 regions: the northern, central, southern, and other regions (i.e., eastern and outlying islands).

2.4. Statistical analysis

We used SPSS software version 19.0 (SPSS Inc., Chicago, IL) for our statistical analysis and SQL Server 2008 (Microsoft Cooperation, New Mexico) for data management. A chi-square test was used to analyze the descriptive data including the demographic characteristics, age, geography, level of urbanization, and comorbidities between the scabies and nonscabies control group. The Cox proportional hazards regression models were performed to estimate the effects of risk factors on the hazard ratio with an accompanying 95% confidence interval (CI). All models were adjusted for the covariates (i.e., gender, age, income, geography, urbanization, and comorbidities) to calculate the independent risks of individual diseases. A 2-sided $P < .05$ was set as the determinant of statistical significance.

3. Results

From January 2001 to December 2006, 2137 children with a scabies infection were identified from the LHID2000 database. Another 8548 matched uninfected children were assigned to the control group, and a total of 10,685 patients were enrolled in our study (Fig. 1). The demographic and medical characteristics of both groups are shown in Table 1. Boys and school-aged children had a higher risk of scabies infection, but the difference was not statistically significant. Most patients were residents of northern Taiwan and urbanized areas. Higher comorbid asthma and atopic dermatitis were observed in scabies group (asthma: scabies vs control groups: 14.8% vs 13%, $P < .05$; atopic dermatitis: scabies vs control groups: 14.6% vs 8.6%, $P < .001$).

All enrolled children were tracked for 7 years to evaluate the incidence of psychiatric disorders, the results of which are summarized in Table 2. A total of 607 (5.68%) children developed a psychiatric disorder in the subsequent 7-year follow-up period. The risk of developing any kind of PDC is not different between scabies and control groups. Patients with scabies had higher risk of developing ID (adjusted hazard ratio [aHR]: 2.04; 95% CI: 1.25–3.32). The prevalence of anxiety, schizophrenia, tic disorder, developmental delay, OCD, conductive disorder, emotional disorder, enuresis, ADHD, and autism was not significantly different between these 2 groups according to the results of the Cox risk regression analysis.

4. Discussion

Based on the clinical similarities in the presenting symptoms, socioeconomic status, immunopathology, and age at onset, we

Table 1
Demographic data in both scabies and control groups.

Variables	Scabies (N, %) 2137 (100%)	Controls (N, %) 8548 (100%)	P
Gender			1
Female	817 (38.2%)	3268 (38.2%)	
Male	1320 (61.8%)	5280 (61.8%)	
Age			1
0–2	101 (4.7%)	404 (4.7%)	
3–5	316 (14.8%)	1264 (14.8%)	
6–12	775 (36.3%)	3100 (36.3%)	
13–18	945 (44.2%)	3780 (44.2%)	
Geography			<.001*
North	1018 (47.6%)	4275 (50.0%)	
Central	326 (15.3%)	1690 (19.8%)	
South	604 (28.3%)	2367 (27.7%)	
Other	189 (8.8%)	216 (2.5%)	
Urbanization			<.001*
1 (highest)	703 (32.9%)	3670 (42.9%)	
2	599 (28.0%)	2326 (27.2%)	
3	481 (22.5%)	1812 (21.2%)	
4 (lowest)	354 (16.6%)	740 (8.7%)	
Comorbidity			
Asthma	317 (14.8%)	1108 (13.0%)	<.05*
Atopic dermatitis	311 (14.6%)	735 (8.6%)	<.001*
Allergic rhinitis	872 (40.8%)	3478 (40.7%)	.922
Preterm	2 (0.1%)	7 (0.1%)	.868

* $P < .05$.

hypothesized that an infection with scabies during childhood may increase the subsequent risk of psychiatric disorders in adolescents. We found there was no obvious difference in the overall incidence of PDC, but children with scabies had a higher risk of developing ID (aHR: 2.04; 95% CI: 1.25–3.32).

ID, used to be called mental retardation, is a neurodevelopmental disorder characterized by limitations in intelligence and adaptive skills since the childhood. ID is associated with several risk factors, such as lower level of maternal education, maternal age of delivery, male sex, and lower birth weight, but the full-spectrum of the underpinning pathophysiology remains largely unclear. Comorbidities with genetic and metabolic diseases are common in patients with ID. Immune-mediated inflammatory processes also contribute to the pathophysiology of ID. In patients with ID, higher level of interleukin (IL)-6 and IL-10 were observed.^[21–23] Genetic abnormalities of IL-1 receptor among patients with X-linked ID were reported.^[24–26] Cytokines are responsible for signaling and can affect hypothalamic–pituitary–adrenal axis and the function of glia in the developing brain.^[12] Exposure to external infection can predispose or increase the susceptibility of an individual to future mental illness via the actions of cytokines and subsequent inflammatory cascades.^[12] Physical diseases can interfere with mental illness and altered cytokine profiles are noted in both psychiatric disorders and scabies (Table 3). In patients with anxiety, elevated levels of tumor necrosis factor α , IL-6, and IL-17 have been reported.^[27–29] In particular, decreased levels of IL-2, IL-4, IL-5, interferon- γ have been found in patients with anxiety.^[29] In children with ADHD, higher serum levels of IL-6 and IL-10 have been detected.^[30–32] Patients with scabies also exhibit increased levels of IL-6, IL-10, and IL-17.^[33–37] Based on similar pathophysiologic underpinnings, an interaction between scabies and psychiatric disorders may occur. The exact mechanism between the association of scabies of ID was unknown but

Table 2
The association between scabies and PDC analyzed by Cox regression.

Psychiatric disorders	Scabies (N, %)	Controls (N, %)	Crude HR (95% CI)	Adjusted HR (95% CI)*
All kinds of PDC	122 (5.7%)	485 (5.7%)	1 (0.82–1.22)	
Anxiety	53 (2.5%)	190 (2.2%)	1.12 (0.82–1.51)	
Schizophrenia	4 (0.2%)	21 (0.2%)	0.76 (0.26–2.22)	
Intellectual disability	27 (1.3%)	48 (0.6%)	2.26 (1.41–3.62)†	2.04 (1.25–3.32)†
Tic disorder	3 (0.1%)	26 (0.3%)	0.46 (0.14–1.52)	
Delayed development	18 (0.8%)	88 (1.0%)	0.82 (0.49–1.36)	
OCD	6 (0.3%)	12 (0.1%)	2 (0.75–5.33)	
Conductive disorder	4 (0.2%)	13 (0.2%)	1.23 (0.4–3.77)	
Emotional disorder	9 (0.4%)	34 (0.4%)	1.06 (0.51–2.21)	
Enuresis	4 (0.2%)	36 (0.4%)	0.44 (0.16–1.25)	
ADHD	32 (1.5%)	162 (1.9%)	0.79 (0.54–1.15)	
ASD	2 (0.1%)	13 (0.2%)	0.62 (0.14–2.73)	

ADHD = attention deficit/hyperactivity disorder, ASD = autism spectrum disorder, HR = hazard ratio, OCD = obsessive-compulsive disorder, PDC = psychiatric disorders in childhood.

* Each variable was adjusted for every other variable.

† $P < .05$ for comparison between patients with 2 groups.

Bold values means a statistically significance in adjust HR.

elevated IL-6 and IL-10 were observed in both scabies and ID. Furthermore, both scabies and ID are thought to be more common in patients with a lower socioeconomic status and in crowded environment according to previous reports.^[14,16] Our study found an 104% increased risk of ID in patients with scabies. Further studies are warranted to elucidate the entire mechanism and casual relationship.

The relationship between scabies and ID may be bidirectional. They share several abovementioned similarities in clinical risk factors and cytokines alterations thus an interaction between scabies and ID may exist. However, the definite mechanism remains largely unclear. Patients with ID may have poor skills of care and are prone to be infected with scabies.^[38] Lower maternal education level is a risk factor of ID and an unsatisfied hygiene may increase the risk of scabies. Moreover, patients ID may have a longer stay in medical institutions, and scabies is relatively common in some institutions.^[11] Although our study confirms an increased risk of ID in patients with scabies, the entire mechanism is complex and further studies are warranted. We suggest a more comprehensive management in treating patients with scabies or ID. Early and comprehensive treatment of scabies and other risk factors may decrease the risk of subsequent ID. When we approach patients with ID, concurrent evaluation of scabies infection and other risk factors may contribute to successful management.

There was no statistical difference of risk for all kinds of PDC between scabies and control group in our study, and underdiagnosis of PDC may contribute to the phenomenon. The diagnosis of PDC is underestimated worldwide. Although at least half of all psychiatric disorders develop before adulthood according to the

Table 3**Comparison of cytokine alterations in patients with anxiety, ADHD, ID or scabies with healthy controls.**

Reference	IL1b	IL1Ra	IL2	IL4	IL5	IL6	IL8	IL10	IL17	TNF- α	IFN- γ	hsCRP	TGF- β	Corti-sol
Anxiety														
Vieira et al ^[29]	↗		↓	↓	↓	↗		↓	↑	↑	↓		-	
O'Donovan et al ^[28]						↑						-		↓
Glaus et al ^[27]	-					-				-		↘		
ADHD														
Segman et al ^[32]		↑												
Oades ^[31]			↑			↑					↑			
Donfrancesco et al ^[30]			-	-		↑		↑	-	-	-			
ID														
Lehtimaki et al ^[22]						↑								
Marek et al ^[23]								↑						
Aureli et al ^[21]		↑				↑								
Scabies														
Mullins et al ^[36]						↑	↓							
Walton and Oprescu ^[37]			↑	↑							↑			
Liu et al ^[34]										↑				
Mounsey et al ^[35]			↗	↗		↗				↑			↗	
Abd El-Aal et al ^[33]								↑						

ADHD = attention deficit/hyperactivity disorder, hsCRP = high-sensitivity C-reactive protein, ID = intellectual disability, IFN- γ = interferon- γ , IL = interleukin, IL1Ra = interleukin 1 receptor agonist, TGF- β = transforming growth factor β , TNF- α = tumor necrosis factor α , TNFR1 = tumor necrosis factor receptor 1. "↑": significantly higher level than healthy controls. "↗": trend of higher cytokine level than healthy controls. "-": no significant difference compared with healthy controls. "↘": trend of lower cytokine level than healthy controls.

World Health Organization's World Mental Health Survey Initiative, the reported prevalence varies according to the specific region of study.^[18,39,40] The clinical manifestations of PDC may be vague and present as many physical illnesses. Variables including, family, school, socio-environmental, cultural factors, and study methodology will affect the occurrence and incidence of reported psychiatric disorders. Thus, the reported prevalence of PDC differs according to each area and study, some of which are summarized in Table 4. In Mexico, 37.9% of adolescents experienced some form of psychiatric disorder and 28.4% sought medical services during the 8-year follow-up period.^[39] The overall prevalence of PDC was 19.9% and 29.7% in high-risk groups in Brazil.^[41] Among British children aged from 5 to 15 years old, 10% were estimated to have psychiatric disorders during late 20th century.^[7] In a recent meta-analysis investigating the worldwide prevalence of mental disorders in children and adolescents, the global pooled prevalence of childhood psychiatric disorders was 13.4%.^[8] The variation of the reported prevalence in different countries is significant.^[8,39,41-43] Therefore, it remains a challenge for pediatricians and psychiatrists to make a diagnosis in children. The incidence of all types of psychiatric disorders during the 7-year follow-up period in the present study was 5.68%. Compared with the 8-year incidence reported by Benjet et al in Mexico, they are quite different (37.9% vs 5.68%, 8-year incidence vs 7-year incidence). Anxiety

disorders and ADHD are the most common psychiatric disorders, which is consistent with the results of most previous studies.^[8,10] Very few patients were diagnosed with tic disorders, OCD, conduction disorders, and emotional disorders; however, we believe that these incidences are underestimated.

The stigmatization of psychiatric disorders may decrease the drive for patients and parents to seek medical assistance.^[45,46] This phenomenon is more evident in traditional conservative Chinese society as patients with psychiatric disorders will be labeled and rejected by their peers. Therefore, individuals who are suspected to have such diseases are more reluctant to seek medical assistance in Taiwan. In addition, doctors are more cautious when making such diagnoses for it may cause negative effects on the patient's personal medical insurance. Therefore, all of these factors result in the underestimation of childhood psychiatric disorders.

4.1. Limitations

Our study is subject to several limitations. First, the diagnosis of NHIRD was categorized according to the ICD-9-CM code. The severity of scabies and psychiatric disorders may affect the risk and is not to be differentiated in the coding system. In addition, children with mild psychiatric disorders may not be recorded, and thus, the diagnosis is underestimated. Second, the onset of

Table 4**Reported prevalence of PDC in different areas.**

Reference	Region	Study period	Age groups, y/o	Any disease, %	Anxiety, %	ADHD, %
Meltzer et al ^[7]	UK	1999	5-15	10	4	
Costello et al ^[42]	USA	1993-2000	9-13	13.3	2.4	0.9
Gau et al ^[43]	Taiwan	1994-1997	13-15	14.8-20.3	3.1-9.2	3.3-7.5
Yang et al ^[44]	China	2008	6-17	9.49	6.06	0.84
Salum et al ^[41]	Brazil		7-14	26	3.7	10.9
Polanczyk et al ^[8]	Meta-analysis	1985-2006	4-18	13.4	6.5	3.4
Benjet et al ^[39]	Mexico	2005-2013	12-17	37.9	7	0

ADHD = attention deficit/hyperactivity disorder.

various psychiatric disorders is variable. For example, anxiety occurs earlier in life, and mood disorders emerge during late adulthood.^[8,13,39] Although a 7-year follow-up period is not short, some prevalent psychiatric disorders do not reach the peak age of onset during this period. Furthermore, the NHIRD is representative of the general population with a broad coverage, but the detailed history and laboratory tests are undistinguishable. Therefore, it is difficult to reach a definite conclusion regarding the casual pathophysiology between scabies and childhood psychiatric disorders. We found an increased risk of ID in patients with scabies but it's impossible to validate the relationship and investigate the pathologic mechanism between these 2 diseases. However, we provided a possible clue and starting point for further studies. Further studies are warranted to elucidate the entire mechanism and casual relationship. Moreover, some risk factors may contribute to the subsequent development of psychiatric disorders, such as childhood adversity or maltreatment.^[41,47] This information is not available due to the limitations of the NHIRD.

5. Conclusion

In conclusion, physical illnesses could interact with psychiatric disorders. This nationwide population-based cohort study provides evidence indicating a possible relationship between scabies and psychiatric disorders during childhood. Although lack of association of scabies and all kinds of PDC was observed, a 104% increased risk of ID was found in children with scabies (aHR: 2.04). We suggest a more comprehensive management in treating patients with scabies or ID. Early and comprehensive treatment of scabies and other risk factors may decrease the risk of subsequent ID. When we approach patients with ID, concurrent evaluation of scabies and other risk factors may contribute to successful management.

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